VALUE IN HEALTH 17 (2014) 307–309

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

COMMENTARY

Questioning Patient Subgroups for Benefit Assessment: Challenging the German Gemeinsamer Bundesausschuss Approach

Jörg Ruof, MD, MPH, MBA[1,2,*], *Charalabos-Markos Dintsios, PhD, MPH*[3,4], *Friedrich Wilhelm Schwartz, MD*[2]

[1]*Roche Pharma AG, Grenzach-Wyhlen, Germany;* [2]*Hannover Medical School, Hannover, Germany;* [3]*German Association of Research-based Pharmaceutical Companies (vfa), Berlin, Germany;* [4]*Department of Public Health, Heinrich Heine University, Düsseldorf, Germany*

Containment of Health Care Costs as a Driver for Patient Subgroups

In Germany, starting in 2011, legislation gave new critical importance to benefit assessments through the Act on the Reform of the Market for Medicinal Products (Arzneimittelneuordnungsgesetz [AMNOG]) [1,2], which was designed to better regulate reimbursement and reduce national health care costs. The German Federal Joint Committee (Gemeinsamer Bundesausschuss [G-BA]) and the Institute for Quality and Efficiency in Health Care (Institut für Qualitätssicherung und Wirtschaftlichkeit im Gesundheitswesen [IQWiG]) are charged with evaluating a drug's added therapeutic value in comparison to an appropriate comparative treatment. IQWiG acts as the scientific review body that evaluates the evidence and recommends the extent of additional benefit. G-BA is the decision maker in terms of not only additional benefit but also determining the appropriate comparative treatment and additional subgroups for assessment [2]. The benefit decisions of G-BA affect the subsequent price negotiations between the manufacturer and the National Association of Statutory Health Insurance Funds (i.e., GKV-Spitzenverband), and therefore have an enormous impact on health care provision. G-BA and IQWiG set their own methods [3,4] and require significant additional information compared with that generated during regulatory development. One element of this additional information is the assessment of the additional subgroups [5].

G-BA decisions regarding additional benefit claim to be grounded in evidence-based medicine (EBM). EBM, however, should not be used to cut health care costs, as was stated as early as 1996 [6]. Some might argue that subgrouping is more prominent in cost-effectiveness than in clinical effectiveness, thereby being useful in containing national health care budgets [7]. Its ad hoc application in the context of EBM, however, as a means to cut costs carries the risk of misuse of EBM. In this commentary, we draw conclusions from current subgrouping experience in early benefit assessments (EBAs) in Germany. We also challenge the validity of applying subgrouping in the context of EBAs, and whether subgrouping should be used to support decisions of such national importance as drug reimbursement.

Subgrouping Practice from G-BA

Fifty-eight EBAs were finalized up until December 1, 2013. A total of 107 subgroups were differentiated within the EBAs. An additional benefit was assigned to 43 (40.2%) subgroups. No additional benefit was assigned to 64 (59.8%) subgroups.

Sex, age, disease severity, and disease state are the predefined subgroups required by G-BA [8]. Additional subgroups might be assigned as appropriate to target products to patients who benefit most. Specific additional subgroupings were required by G-BA to conduct so-called slicing of populations from, for example, licensing trials (e.g., boceprevir, cabazitaxel, fingolimod, microbial collagenase, telaprevir, and ticagrelor), and also to apply more than one appropriate comparative treatment to different stages of disease/disease entities (e.g., fingolimod, microbial collagenase, ticagrelor, boceprevir, vismodegib, and pertuzumab) [9].

The above reasons to demand ad hoc subgroups may help determine those groups experiencing maximal benefit from a drug, albeit purely in an exploratory context, not in a confirmatory one. Although it is reasonable to exclude those patients not experiencing a true benefit from treatment, the key challenge is how to address those who may possibly experience a true benefit—that is, those possibly without specifically tailored confirmatory evidence.

Conflicts of interest: Jörg Ruof is an employee of Roche Pharma AG. Charalabos-Markos Dintsios is a staff member of the German Association of Research-based Pharmaceutical Companies. Friedrich Wilhelm Schwartz received consultancy fees from Roche Pharma AG and MSD.

* *Address correspondence to:* Jörg Ruof, Roche Pharma AG, Emil-Barrell-Str. 1, 79639 Grenzach-Wyhlen, Germany.
E-mail: joerg.ruof@roche.com.

http://dx.doi.org/10.1016/j.jval.2014.05.001

Questioning the Practice of G-BA and IQWiG

The subgroups in EBAs as determined by G-BA were often questionably small from a statistical perspective and had low credibility. Subgroup analyses were generally conducted post hoc, often not based on plausible hypotheses, lacked biologic rationale, and had a high risk of multiplicity. More specifically:

1. The size of many of the evaluated subgroups was very small, which has implications for statistical power. A clinical trial is not necessarily powered to prove subgroup-treatment interactions. A failure to detect a true treatment effect (type 2 error) is more likely in subgroups because the data are subdivided into smaller data sets, each with a reduced power to detect a treatment effect. For example, G-BA separately analyzed the benefit of boceprevir for treatment-naive patients with hepatitis C and hepatic cirrhosis. The manufacturer in the boceprevir dossier stated that less than 1% of the patients fulfilled those criteria. Furthermore, an estimate provided by the manufacturer showed that approximately 7 patients/year in Germany were identified who experienced hepatic cirrhosis related to hepatitis C, but had not received any specific treatment [9]. Confirmatory statistics on such small patient numbers are inappropriate. In another EBA, G-BA suggested to separately analyze the effect of pertuzumab in patients with nonvisceral breast cancer [9]. A total of 808 patients were enrolled in the respective trial, with 178 of these patients having nonvisceral disease. The assessment of overall survival included a total of 165 deaths, with 33 events occurring in patients with nonvisceral disease. Assuming an equal effect of pertuzumab on visceral and nonvisceral patients, an appropriately powered analysis of nonvisceral patients would also require a trial with approximately 800 patients instead of the 178 patients in the nonvisceral subgroup assessed by G-BA.
   The additional benefit of microbial collagenase to treat Dupuytren's disease, for example, was assessed according to disease burden as determined by Tubiana stages [9]. Only 17 patients (15 active; 2 placebo) of the largest trial and only 1 patient (active) in another trial, however, had the highest Tubiana stage, which accounted for a mere 6% and 2% of the overall trial population, respectively [9]. The subgroup sizes suggested for other EBAs (e.g., fingolimod and vismodegib) were also notably small [9].
2. Many subgroups in EBAs have not been defined a priori and therefore do not constitute confirmatory analyses (e.g., fingolimod, microbial collagenase, and ticagrelor [9]). Furthermore, a high number of subgroups are often tested (e.g., telaprevir, ticagrelor, and boceprevir), increasing the risk of multiplicity [9]. Multiple testing of subgroups increases the chance of an effect being mistakenly classified as a significant treatment effect (type 1 error).
3. Many subgroups separately assessed by G-BA were not characterized by differing treatment effects in the respective Summary of Product Characteristics. For example, the Summary of Product Characteristics does not necessarily suggest different effects of boceprevir according to cirrhosis status or cabazitaxel based on age [10]. Nevertheless, all these subgroups were evaluated separately by G-BA and IQWiG [9].
4. Subgrouping as conducted by G-BA was not necessarily based on a sound biologic rationale. Telaprevir, for example, was shown beneficial in terms of sustained virologic response across patient groups irrespective of cirrhosis status, and the effect of ticagrelor was consistent across acute coronary syndromes as well as randomized treatment pathways [10]. Nevertheless, these additional subgroup assessments were required [9].

Efforts from manufacturers to develop targeted medicines have also not been recognized by G-BA. Ipilimumab and vemurafenib are, for example, both indicated for the treatment of melanomas. Vemurafenib specifically and exclusively targets BRAFV600 mutation-positive melanomas, leading to significant increases in response rates in comparison with nonpersonalized treatments [11]. Nevertheless, both specific and nonspecific treatments have been rated as having significant additional benefit by G-BA [9], without recognizing higher response rates of targeted medicine.

Table 1 – Characteristics of appropriate and inappropriate subgroup analyses for decision making in drug reimbursement (modified from Sun et al. [20]).

Appropriate	Inappropriate
• Tests a hypothesis (confirmatory analysis) • Prospectively defined analyses • Based on biologic rationale or at least solid experience • Small number of prospectively defined subgroups tested (≤ 5)	• No hypothesis (exploratory analysis) • Ad hoc analyses • Controversial biologic rationale; no experience • High number of ad hoc subgroups (>5): increased risk of multiplicity

Future Outlook for Appropriate Subgroup Analyses

The credibility of subgroup analyses has generally been questioned and, if performed inappropriately, can be extraordinarily misleading [12–16]. Therefore, subgroup assessments in the framework of EBAs should follow internationally established guidelines and respective publications for appropriate analyses [17–20]. Considerations for the development of an appropriate framework for such analyses are listed in Table 1, and also include the following:

1. Decisions on reimbursement should preferably be based on statistically powered, prospectively defined analyses and populations.
2. If subgroup analyses are conducted, a biologic rationale should be given (or at least be based on solid experience) and corresponding stratification factors should be defined at study randomization. In the absence of confirmatory subgroup evaluations, the best estimate of an effect should be from the overall population [17].
3. G-BA and IQWiG advice on required subgroup analyses should be shifted to earlier in the regulatory process, that is, into phase II-III development [21]. At present, this advice is usually given after finalization of the phase III program (1 year before market authorization). The more recent possibility of joint advice from G-BA and regulatory authorities could be an important step forward toward harmonizing market authorization and market access requirements [22].
4. An additional approach focusing on personalized medicine to target treatments to those experiencing the most therapeutic benefit comes from the German Ministry of Education and Research [23]. Results from well-conducted and purpose-driven research on personalized medicine should be recognized by the G-BA as a suitable option to efficiently and ethically target treatments.

Conclusions

Ad hoc subgroup analyses from G-BA and IQWiG are not appropriate for making national drug reimbursement decisions.

Underpowered, nonprospectively defined slicing procedures seek to decrease the size of reimbursed indications and thereby exclude patients who may experience benefit from treatment. Thus, subgroup analyses are ethically disputable because they may lead to biased treatment decisions. Such slicing procedures abuse EBM. Although pioneers of EBM recognized that EBM could provide useful information even in the face of deepening concerns about health care costs [24], they warned that such information might be used to inappropriately cut costs [6]. Consequently, subgrouping standards specific to AMNOG are urgently needed, and joint G-BA/regulatory advice earlier in the drug development process is desirable.

Source of financial support: Medical writing services were provided by nspm ltd, Meggen, Switzerland, with financial support from Roche Pharma AG.

REFERENCES

[1] Federal Ministry of Health. The Act on the Reform of the Market for Medicinal Products (Gesetz zur Neuordnung des Arzneimittelmarktes - AMNOG). Available from: http://www.bmg.bund.de/ministerium/english-version/health/amnog.html. [Accessed November 22, 2013].
[2] Ruof J, Schwartz FW, Schulenburg JM, Dintsios CM. Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation. Eur J Health Econ 2013. http://dx.doi.org/10.1007/s10198-013-0495-y. [Epub ahead of print].
[3] IQWiG. General Methods 4.0. Available from: https://www.iqwig.de/download/General_Methods_4-0.pdf. [Accessed November 22, 2013].
[4] G-BA. Verfahrensordnung [in German]. Available from: http://www.g-ba.de/institution/auftrag/Verfahrensordnung/. [Accessed June 12, 2013].
[5] Rychlik R. Target patient populations: how does the regulatory and reimbursement view differ? Insights from the German IQWiG. J Public Health 2013;21:109–14.
[6] Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: what it is and what it isn't. BMJ 1996;312:71–2.
[7] Sculpher M. Subgroups and heterogeneity in cost-effectiveness analysis. Pharmacoeconomics 2008;26:799–806.
[8] G-BA. Format und Gliederung des Dossiers, einzureichende Unterlagen, Vorgaben für technische Standards (Modul 4) [in German]. Available from: http://www.g-ba.de/institution/themenschwerpunkte/arzneimittel/nutzenbewertung35a/anlagen/. [Accessed December 10, 2013].
[9] G-BA. Übersicht der Wirkstoffe [Overview of products]. Available from: http://www.g-ba.de/informationen/nutzenbewertung/. [Accessed November 22, 2013].
[10] European Medicines Agency. Summary of product characteristics. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124. [Accessed June 5, 2013].
[11] Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.
[12] Petticrew M, Tugwell P, Kristjansson E, et al. Damned if you do, damned if you don't: subgroup analysis and equity. J Epidemiol Community Health 2012;66:95–8.
[13] Sleight P. Debate: subgroup analyses in clinical trials: fun to look at – but don't believe them! Curr Control Trials Cardiovasc Med 2000;1:25–7.
[14] van Gijn J. Extrapolation of trials data into practice: where is the limit? Cerebrovas Dis 1995;5:159–62.
[15] Rothwell PM. Treating individuals 2 – subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005;365:176–86.
[16] Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. Lancet 2000;355:1064–9.
[17] Moye LA. Rudiments of subgroup analyses. Prog Cardiovasc Dis 2012;54:338–42.
[18] ICH harmonised tripartite guideline. Statistical principles for clinical trials – E9. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf. [Accessed June 5, 2013].
[19] Committee for Proprietary Medicinal Products. Points to consider on multiplicity in clinical trials. Biometrical J 2001;43:1039–48.
[20] Sun X, Briel M, Busse JW, et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. BMJ 2012;344:e1553–62.
[21] European Medicines Agency. Early dialogue between regulators and health technology assessment bodies key to medicines development. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/11/news_detail_001979.jsp&mid=WC0b01ac058004d5c1. [Accessed December 10, 2013].
[22] Federal Ministry of Health. Der Deutsche Bundestag beschließt Vorschriften zur Verbesserung der Arzneimittelsicherheit und Arzneimittelversorgung [in German]. Available from: http://www.bmg.bund.de/fileadmin/dateien/Pressemitteilungen/2012/2012_02/120628_PM_48_AMG_Novelle_BT_2-3_Lesung_01.pdf. [Accessed June 5, 2013].
[23] Federal Ministry of Education and Research. Aktionsplan Individualisierte Medizin - Ein neuer Weg in Forschung und Gesundheitsversorgung [in German]. Available from: http://www.bmbf.de/pub/BMBF_Aktionsplan_IndiMed.pdf. [Accessed June 3, 2013].
[24] Gordon G, Cairns J, Churchill D, et al. Evidence-based medicine: a new approach to teaching the practice of medicine. JAMA 1992;268:2420–5.